Northern blots, cDNA library screening, and RACE. Multiple-tissue (cat. #7760-1) and Human Brain II (cat. #7755-1) Northern blots were purchased from Clontech and hybridization was carried out as recommended by the supplier. The transcript A specific probe was generated using PCR primers 266F (SEQ ID NO: 11) (5'-CGGCACGAGGATTATTCAAG-3') and GSP3 (5'-GCTCGGGTACTGAGGTCTG-3') (SEQ ID NO: 12) which amplified an 190 bp fragment from cDNA clone 266552 (Figure 3). The transcript B specific probe was derived using PCR primers AA490925F (5'-AGTTGTTACACAGGGTTGTTGG-3') (SEQ ID NO: 13) and AA490925R (5'-AGGCTGTACATCAGACAGAAGG-3') (SEQ ID NO: 14) which amplified an 373 bp segment from cDNA SFB14 (Figure 3). We have sequenced the HTF-island shown in Figure 1B at the 5'-end of EPM2A.

On page 22, delete the second full paragraph, and replace this paragraph with the following in accordance with 37 C.F.R. § 1.121. A marked up version showing changes is attached:

Mutation Analysis. Mutations were detected by radioactive cycle sequencing using the Thermosequenase Kit (Amersham Life Science) with Qiagen column purified PCR products. The combinations of PCR primer pairs used were JRGXBCF (5'-TCCATTGTGCTAATGCTATCTC-3') (SEQ ID NO: 15) and JRGXBCR (SEQ ID NO: 16) (5'-TCAGCTTGCTTTGAGGATATTT-3'); product size 310 bp, 824F (5'-GCCGAGTACAGATGCTGCC-3' (SEQ ID NO: 17) and 824R (SEQ ID NO: 18) (5'-CACACAGTCCTTTCAGTTCAGG-3'); product size 384 bp, and H1F (5'-GAATGCTCTTTCCACTTTGC-3' (SEQ ID NO: 7) and 824R; product size 587 bp. The position of the primers are shown in Figure 3.

On page 25, delete the first full paragraph, and replace this paragraph with the following in accordance with 37 C.F.R. § 1.121. A marked up version showing changes is attached:

The protein encoded by EPM2A contains an amino acid motif (Figure 1C) that corresponds with the consensus sequence (SEQ ID NO: 22), HcxxGxxRS(T), of the catalytic site of PTPs. In addition to the essential cysteine and arginine residues found in all PTPs (Figure 4C), EPM2A contains the expected aspartic acid necessary for

B8 Cont'd completion of the catalytic reaction, positioned 31-aa N terminal of the cysteine nucleophile.

On page 25, delete the third full paragraph, and replace this paragraph with the following in accordance with 37 C.F.R. § 1.121. A marked up version showing changes is attached:

B9 The deduced amino acid sequence of the newly identified protein(s) indicated that transcripts A, B, C and D encode a 9 amino acid motif (Figure 4A) that corresponds exactly to the consensus sequence (SEQ ID NO: 22), HCxxGxxRS(T), of the active catalytic site of protein tyrosine phosphatases (PTPs) (14,15). So far, no other structural motifs could be identified, and from the sequence it is not apparent if this protein belongs to the receptor-like PTPs, the intracellular PTPs, or the dual specificity phosphatases (DSPs) which dephosphorylate both tyrosine and serine/threonine residues (16). The identification of the EPM2A gene as a putative PTP provides the first clue to understand the basic defect.

On page 25, delete the last full paragraph, and replace this paragraph with the following in accordance with 37 C.F.R. § 1.121. A marked up version showing changes is attached:

B10 At the HTF-island shown in Figure 3, we have identified through GRAIL analysis (http://compbio.ornl.gov) an additional putative exon 189 nucleotides in length. An ATG (AUG) triplet is present at the beginning of this predicted ORF and the nucleotide sequence (SEQ ID NO: 23) surrounding the consensus sequence (CCCGCCAUGC) has the proposed features of the consensus sequence (SEQ ID NO: 24) (GCCA/GCCAUGG) of a eukaryotic translation initiation site (12). The predicted start exon maintains open reading frame with the most 5′ sequence of transcript A and this combined stretch of 298 nucleotides contains exon/intron junction sequences with splice sites that confirm with the consensus in other mammalian genes. If the predicted exon is part of EPM2A, transcript A would be predicted to be 317 amino acids long.

On page 26, delete the first full paragraph under the title "**EPM2A Mutations**", and replace this paragraph with the following in accordance with 37 C.F.R. § 1.121. A marked up version showing changes is attached:

Using the available genomic structure for the gene, the inventors' screened an affected member from each of 30 Lafora families for mutations by direct DNA sequencing. A total of 14 mutations were detected consisting of 12 different DNA sequence alterations and 2 microdeletions. The mutations are summarized in Table 3. The mutation from C to A at position -12 refers to a mutation that occurs 12 bases upstream from the ATG start codon in Figure 13. Some of the sequence upstream of the ATG is as follows:

(SEQ ID NO: 19) ... gccgggtattcgcgccgCcgccgcccgccATG...

The mutation site at -12 is indicated with a capital C. To date, mutations have been found in 65% of EPM2A families. Some of the mutations are discussed below

B11

On page 26, delete the second full paragraph, and replace this paragraph with the following in accordance with 37 C.F.R. § 1.121. A marked up version showing changes is attached:

Two mutations that, based on the current consensus sequences were specific for transcript A, could be detected. Family LD-5 contained a homozygous C to T point mutation which resulted in an arginine to cysteine change affecting a region of unknown function. To test for the presence of the C to T point mutation in family LD-5 in the unaffected population PCR was completed on 54 samples (108 chromosomes) using JRGXBF and JRGXBR primers and the product was blotted in duplicate. One membrane was hybridized with a wild type oligonucleotide (ATCATGACCGTTGCTGTAC) (SEQ ID NO: 20) and the other with LD5 mutant (TCATCATGACTGTTGCTGTAC) (SEQ ID NO: 21) oligonucleotide at 42°C (washing with 5X SSC at room temperature for 20 minutes followed by 2X SSC 20 minutes at 65°C). No mutant alleles were found.

B12

On page 28, delete the first paragraph after the title **"Patients and methods"**, and replace this paragraph with the following in accordance with 37 C.F.R. § 1.121. A marked up version showing changes is attached:

Patients reported here had biopsy-proven Lafora's disease. Polymerase chain reaction (PCR) primer sequences and conditions were:

JRGXBF: (SEQ ID NO: 9) 5'-TCCATTGTGCTAATGCTATCTC-3',

JRGXBR: (SEQ ID NO: 10) 5'-TCAGCTTGCTTTGAGGATATTT-3',

H1F: (SEQ ID NO: 7) 5'-GAATGCTCTTTCCACTTTGC-3,

B13

B13 Cont'd

PTPR: (SEQ ID NO: 8) 5'-GGCTCCTTAGGGAAATCAG-3';
Annealing: 62°; [MgC12] = 1.25mM. Stock DNA was used; PCR products were purified on Qiagen columns. Restriction digests were performed at 37°, and products were run on 3% agarose gels.

IN THE CLAIMS:

In accordance with 37 C.F.R. § 1.121, please substitute for original claims 10, 12 and 15 the following rewritten versions of the same claims, as amended. The changes are shown explicitly in the attached "Version With Markings to Show Changes Made."

B14

10. (Amended) A method according to claim 9 wherein the C to T change is detected by a method comprising:

(a) amplifying the nucleic acid sequences in the sample with primers H1F (5'-GAATGCTCTTTCCACTTTGC-3) (SEQ ID NO: 7) and PTPR (5'-GGCTCCTTAGGGAAATCAG-3') (SEQ ID NO: 8) in a polymerase chain reaction;

(b) digesting the amplified sequences with the restriction endonuclease *HaeIII*; and

(c) determining the size of the digested sequences wherein the presence of a fragment of approximately 199bp indicates the sample is from an animal with Lafora's disease or an animal that is a carrier of Lafora's disease.

B15

12. (Amended) A method according to claim 11 wherein the G to A change is detected by a method comprising:

(a) amplifying the nucleic acid sequences in the sample with primers H1F (5'-GAATGCTCTTTCCACTTTGC-3) (SEQ ID NO: 7) and PTPR (5'-GGCTCCTTAGGGAAATCAG-3') (SEQ ID NO: 8) in a polymerase chain reaction;

(b) digesting the amplified sequences with the restriction endonuclease *Pst1*; and

(c) determining the size of the digested sequences wherein the presence of at least one fragment of approximately 520bp indicates that the sample is